American Journal of Medical Genetics 92:273–277 (2000)

New Case of Cole-Carpenter Syndrome

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We describe a girl with a severe progressive type of osteogenesis imperfecta, in association with multisutural craniosynostosis, growth failure, and craniofacial findings including ocular proptosis, marked frontal bossing, midface hypoplasia, and micrognathia. Collagen analysis was normal. These features are consistent with the diagnosis of Cole-Carpenter syndrome. This report provides further evidence for the existence of this rare genetic entity. Am. J. Med. Genet. 92:273–277, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: osteogenesis imperfecta; skeletal dysplasia; craniosynostosis; growth retardation; osteoporosis

INTRODUCTION

Osteogenesis imperfecta (OI) is a clinically and biochemically heterogeneous disorder characterized by bone fragility and osteopenia. Four main groups are defined [Sillence et al., 1979]. Each is associated with abnormalities of type I collagen, although clinical and genetic heterogeneity exists within each group. In addition, there are a number of rare variants of OI, including the osteoporosis-pseudoglioma syndrome [Gong et al., 1996], the syndrome of osteopenia with radiolucent lesions of the mandible [Levin et al., 1985], and OI with congenital joint contractures (Bruck syndrome) [Bank et al., 1999].

In 1987, Cole and Carpenter [1987] described a new variant of OI, which has since become known as Cole-Carpenter syndrome. In addition to severe bone fragility, the main features of the syndrome are craniosynostosis, communicating hydrocephalus, ocular proptosis, marked postnatal growth failure, and distinctive facial appearance. Three other cases have since been reported with features suggestive of Cole-Carpenter syndrome [MacDermot et al., 1995; Marwaha et al., 1993; Stopfer et al., 1992], but all of these cases have included important differences compared with the original report, bringing into question the existence of Cole-Carpenter syndrome as a distinct entity. We report a previously undescribed child with clinical features remarkably similar to the initial two cases.

CLINICAL REPORT

The female infant was the first child of healthy unrelated parents. A routine ultrasound examination at 18 weeks gestation revealed long bones below the 10th centile in length. The child was born by vaginal delivery at 37 weeks of gestation. The birth weight was 2.1 kg (<3rd centile) with a length of 42.5 cm (<3rd centile) and head circumference (OFC) of 32.0 cm (3rd centile). Mild respiratory distress was treated with 35% oxygen. She was noted to have unusual facial features comprising down-slanting palpebral fissures, micrognathia, and a "sunset" eyes appearance. X-rays showed osteopenia and bowing of long bones consistent with OI and a unilateral rib fracture was noted. Cranial ultrasound showed normal ventricles and a mild germinal matrix hemorrhage. Calcium, phosphate, and alkaline phosphatase levels were normal, and chromosomes were 46,XX.

The infant was reassessed at age 8 months (Fig. 1). She exhibited startling growth failure. Her weight was only 4.4 kg, her length was 58 cm (both far below 3rd centile), and her head circumference was 42 cm (3rd centile). The abnormal craniofacial features had become more apparent, with prominent "sunset" eyes and epicanthus inversus. There was brachycephaly and turricephaly with marked frontal bossing, suggestive of craniosynostosis. Hypermobile joints and blue sclera were also noted. On examination of her skull, a sagittal ridge of bone was present, with temporal ossification deficient bilaterally and no anterior fontanelle palpable. She had poor head control and significant gross motor delay, but fine motor and social development were normal. Dental eruption occurred at age 12 months, revealing dentinogenesis imperfecta.

By age 14 months she had sustained two long bone fractures, both with minor trauma. Treatment with bisphosphonate (intravenous pamidronate, 1 mg/kg/day for 3 days at 4-month intervals) was commenced at age 21 months, and there have been no further fractures at follow-up to age 30 months.

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Received 24 January 1999; Accepted 31 January 2000

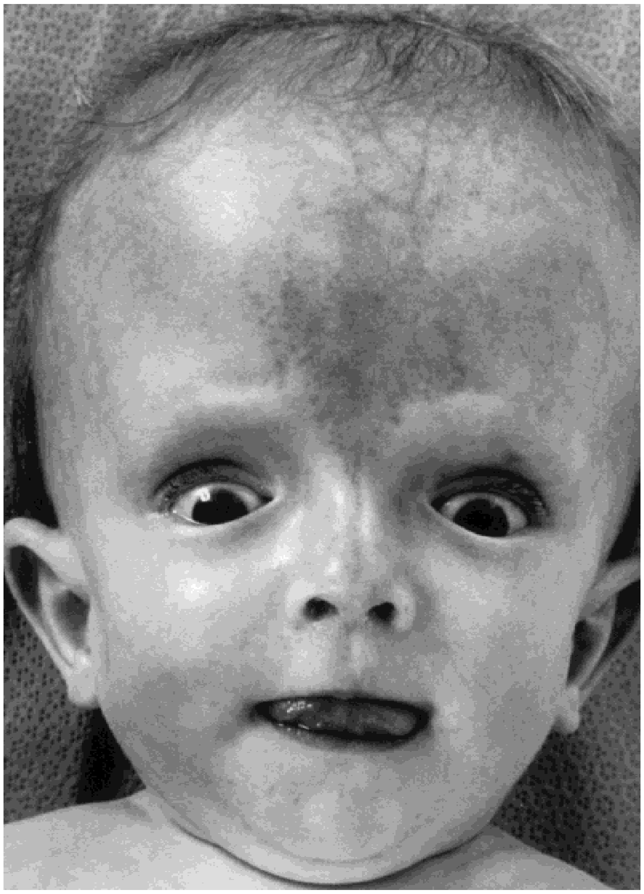

Fig. 1. The girl at age 8 months. Note the sunset eyes, frontal bossing, micrognathia, and prominent superficial hemangioma, which has faded with age.

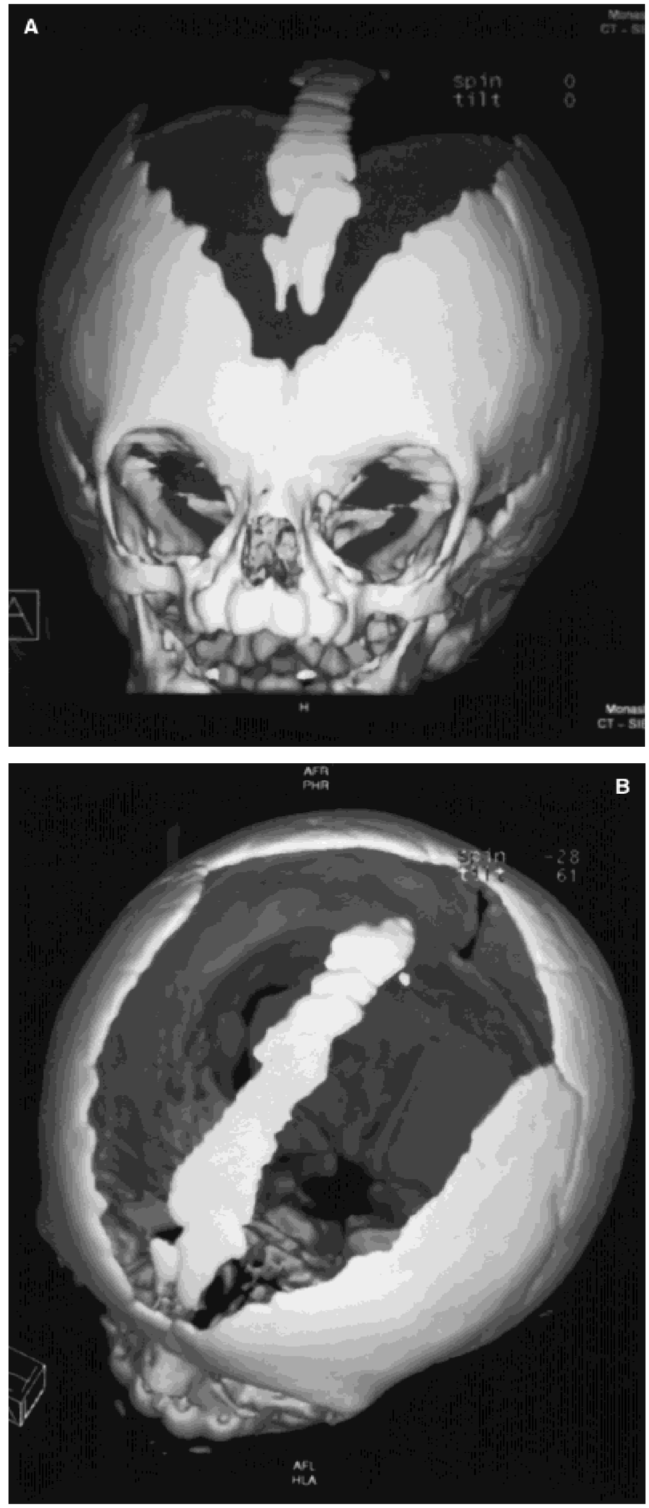

Fig. 2. 3-D CT reconstruction of the skull vault (**A**,**B**), demonstrating craniosynostosis of all sutures except the posterior sagittal suture, and a large U-shaped defect in the bilateral frontoparietal bones.

Radiological Findings

X-rays of all bones showed marked generalized osteopenia (Fig. 3A–D). The skull was brachyturricephalic with multiple wormian bones, shallow orbits, and poorly formed teeth. There was marked osteopenia of the vertebral bodies, and the vertebrae of the thoracolumbar region were abnormal, with inferior irregularity and anterior rounding of several vertebrae. The ilia were rounded with narrow sacroiliac notches and hypoplastic acetabular roofs. The pubis and ischia were normal. The long bones were short and bowed, with several fractures noted, and all metaphyses were widened and irregular. The long bone epiphyses were normal in appearance. The short tubular bones of the hands were normally modeled, but metaphyseal cupping was present in the distal metacarpals and proximal phalanges. The metaphyseal portions of the ribs were expanded, further suggesting a metaphyseal component of this skeletal dysplasia. The scapulae appeared normal. Bone age was appropriate.

Cranial CT scan confirmed the finding of severe osteopenia and multiple wormian bones, and demonstrated craniosynostosis with fusion of the sagittal, lambdoid, coronal, and metopic sutures (Fig. 2). Wide and long pathological fracture of the parietal bones was present on either side of the fused sagittal suture. This was allowing the skull to grow vertically, accounting for the turricephalic appearance and the unusual findings on palpation of the skull. There was no evidence of hydrocephalus.

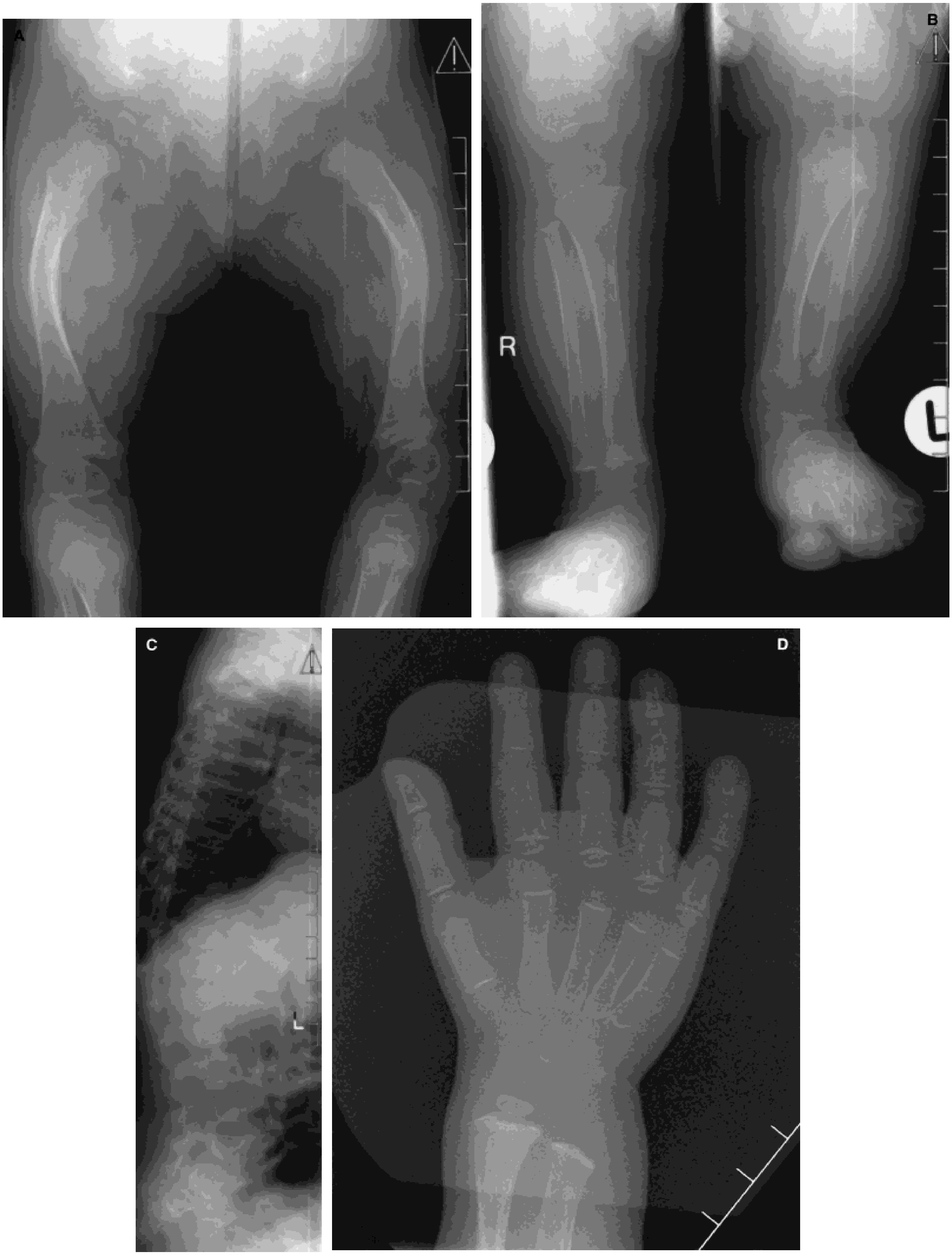

Fig. 3. X-ray examination of the legs (**A**,**B**) demonstrating irregular widened metaphyses, bowing of the femora, and small compression fracture of the distal left fibula, spine (**C**) showing marked osteopenia, anterior rounding and minor irregularity of several vertebrae, and hand (**D**) showing metaphyseal cupping of the distal metacarpals and proximal phalanges .

Collagen and FGFR Studies

Analysis of Type I collagen metabolism was performed on cultured skin fibroblasts as previously described [Bateman et al., 1984]. Synthesis and secretion of Type I collagen was normal, and no abnormality was detected in the electrophoretic migration of the Type I collagen chains. These results suggest that Type I collagen production was normal in quantity and quality. Screening for the FGFR mutations P252R in FGFR1 and P250R in FGFR3 also showed normal results.

DISCUSSION

Cole and Carpenter described two patients in 1987 with an apparently new variant of OI [Cole and Carpenter, 1987]. The main features of the condition were bone fragility, craniosynostosis, hydrocephalus, and a distinctive facial appearance. Both infants were apparently normal at birth, but shortly after developed multiple fractures and postnatal growth retardation. Radiographic changes were characteristic, with numerous metaphyseal irregularities and bowing of the long bones, and the resultant deformities were similar to those seen in the progressive deforming type of OI (Type 3). Collagen studies were normal. The two infants had remarkably similar facial features, with proptosis, marked frontal bossing, midface hypoplasia, and micrognathia. Intellectual performance was normal in both individuals.

Since the original description there have been three further published reports of possible cases of Cole-Carpenter syndrome (Table I), although all three cases differ from the original report in important ways.

The first case was a 5-month-old male infant with communicating hydrocephalus, blue sclera, mild proptosis, and micrognathia [Marwaha et al., 1993]. He had bowing and shortening of the limbs, but no evidence of fractures on X-ray, and at age 5 months craniosynostosis was not documented.

Stopfer et al. [1992] described a number of features of Cole-Carpenter syndrome in a child born at 24 weeks gestation. Features present included craniosynostosis, ocular proptosis, hydrocephalus, marked postnatal growth retardation, blue sclera, dentinogenesis imperfecta, and perinatal fractures. This child also had several features not seen in the original cases of Cole-Carpenter syndrome, including psychomotor retardation, microcephaly, webbing of fingers (2/3 on right and 3/4 on left), partial 2/3 syndactyly of toes, undescended testes, and hypospadius. Only one further fracture was noted beyond the neonatal period, with follow-up to age 7 years. Even allowing for the extreme prematurity, which may have been responsible for some of the features in this case, the evidence suggests that this child had a different clinical syndrome.

The third case was a 4-year-old boy described as a possible mild form of Cole-Carpenter syndrome [MacDermot et al., 1995]. He was born with severe hydrops fetalis and experienced a difficult neonatal course. At follow-up, the child had frontal bossing, communicating hydrocephalus, developmental delay, and osteopenia. A single metaphyseal fracture had occurred shortly after birth, but craniosynostosis was not reported. It was later suggested that the diagnosis in this child was Coffin-Lowry syndrome [Fryns, 1996].

The child reported here is remarkably similar to the

TABLE I. Cases of Cole-Carpenter Syndrome*

	Patient 1 [Cole and Carpenter, 1987]	Patient 2 [Cole and Carpenter, 1987]	Patient 3 [Marwaha et al., 1993]	Patient 4 [Stopfer et al., 1992]	Patient 5 [MacDermot et al., 1995]	Present report
Growth						
Perinatal fractures	−	−	−	+	−	+
Prenatal growth deficiency	−	−	+	−	−	+
Postnatal growth deficiency	+	+	+	+	−	+
Performance						
Language	N	N	D	D	D	N
Fine motor skills	N	N	D	D	D	N
Hypotonia	−	+	+	−	+	+
High-pitched voice	+	+	+			+
Hearing	N	N	N	N		N
Vision	N	N	N	N		N
Craniofacial features						
Craniosynostosis	+	+	−	+	−	+
Communicating hydrocephalus	+	+	+	−	+	−
Ocular proptosis	+	+	+	+	−	+
Dentinogenesis imperfecta	+	−	−	+	−	+
Blue sclera	+	+	+	+	+	+
Micrognathia	+	+	+	+	−	+
Radiographic features						
Metaphyseal fractures	+	+	−	+	−	+
Diaphyseal fractures	+	+	−	+	+	+
Long bone deformities	+	+	+	+	−	+
Wormian bones	+	−	+	+	−	+
Osteopenia	+	+	+	+	+	+
Spondylodysplastic changes	+	+	+		−	+
Kyphoscoliosis	+	+	−	+	−	−

*D, delayed; N, normal.

original two cases of Cole and Carpenter with regard to clinical and radiological features. The main point of difference is that the present case had onset of fractures and growth retardation before birth, whereas in the original cases these features were postnatal in onset. This may simply reflect variability in clinical severity.

The molecular basis of Cole-Carpenter syndrome is yet to be elucidated. The extreme rarity of Cole-Carpenter syndrome raises the question of whether the condition represents a single gene disorder, or whether it might represent the chance association of craniosynostosis and osteogenesis imperfecta. The latter hypothesis is supported by the observation of craniosynostosis occurring as an acquired phenomenon in Type 3 OI [Eppley et al., 1994]. Two points, however, strongly suggest that at least the present case and the cases of Cole and Carpenter represent a single gene disorder; namely, the remarkable similarity in phenotype and the fact that screening for defects in collagen I and FGFR genes has so far been negative in all three cases (D. Cole, personal communication). The inheritance of Cole-Carpenter syndrome has not been determined, with family history being negative in all cases. Heterozygosity for a new autosomal dominant mutation was suggested [Sillence, 1996], but recessive inheritance is another possibility.

Normal collagen studies have also been observed in two other rare variants of OI, Osteoporosis-Pseudoglioma syndrome (OPS) [Somer et al., 1988] and Bruck syndrome [McPherson and Clemens, 1997]. Both of these conditions are autosomal recessive. The molecular defect in Bruck syndrome has recently been identified as a deficiency of bone-specific telopeptide lysyl hydroxylase, resulting in aberrant crosslinking of bone collagen [Bank et al., 1999]. The molecular basis of OPS is unknown, but a disorder of matrix homeostasis rather than matrix structure has been suggested [Gong et al., 1996]. Biglycan, an extracellular matrix proteoglycan, has also been implicated in bone fragility in the setting of normal collagen production. Biglycan-deficient knockout mice demonstrate a skeletal phenotype of reduced growth rate and decreased bone mass [Xu et al., 1998]. It is possible that Cole-Carpenter syndrome may also result from abnormal extracellular processing of collagen molecules.

REFERENCES

Bank RA, Robins SP, Wijmenga C, Breslau-Siderius LJ, Bardoel AF, van der Sluijs HA, Pruijs HE, TeKoppele JM. 1999. Defective collagen crosslinking in bone, but not in ligament or cartilage, in Bruck syndrome: indications for a bone-specific telopeptide lysyl hydroxylase on chromosome 17. Proc Natl Acad Sci USA 96:1054–1058.

Bateman JF, Mascara T, Chan D, Cole WG. 1984. Abnormal type I collagen metabolism by cultured fibroblasts in lethal perinatal osteogenesis imperfecta. Biochem J 217:103–115.

Cole DE, Carpenter TO. 1987. Bone fragility, craniosynostosis, ocular proptosis, hydrocephalus, and distinctive facial features: a newly recognized type of osteogenesis imperfecta. J Pediatr 110:76–80.

Eppley BL, Kalsbeck JE, Sadove AM. 1994. Cranial reconstruction in osteogenesis imperfecta. J Craniofac Surg 5:180–184.

Fryns JP. 1996. Osteopenia, abnormal dentition, hydrops fetalis and communicating hydrocephalus: unusual early clinical signs in Coffin-Lowry syndrome. Clin Genet 50:112.

Gong Y, Vikkula M, Boon L, Liu J, Beighton P, Ramesar R, Peltonen L. 1996. Osteoporosis-pseudoglioma syndrome, a disorder affecting skeletal strength and vision, is assigned to chromosome region 11q12-13. Am J Hum Genet 59:146–151.

Levin LS, Wright JM, Byrd DL, Greenway G, Dorst JP, Irani RN, Pyeritz RE, Young RJ, Laspia CL. 1985. Osteogenesis imperfecta with unusual skeletal lesions: report of three families. Am J Med Genet 21:257–269.

MacDermot KD, Buckley B, Van Someren V. 1995. Osteopenia, abnormal dentition, hydrops fetalis and communicating hydrocephalus. Clin Genet 48:217–220.

Marwaha RK, Sarkar B, Katariya S, Jayshree K. 1993. Cole-Carpenter's syndrome. Indian J Pediatr 60:305–308.

McPherson E, Clemens M. 1997. Bruck syndrome (osteogenesis imperfecta with congenital joint contractures): review and report on the first North American case. Am J Med Genet 70:28–31.

Sillence DO. 1996. Disorders of bone density, volume, and mineralization. In: Rimoin DL, Connor JM, Pyeritz RE, editors. Emery and Rimoin's principles and practice of medical genetics, vol. 2. New York: Churchill Livingstone. p 2817–2835.

Sillence DO, Senn A, Danks DM. 1979. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 16:101–116.

Somer H, Palotie A, Somer M, Hoikka V, Peltonen L. 1988. Osteoporosis-pseudoglioma syndrome: clinical, morphological, and biochemical studies. J Med Genet 25:543–549.

Stopfer H, Hurt A, Magilner A, Schneider A. 1992. A variant type of osteogenesis imperfecta: confirmation of a rare phenotype. Am J Hum Genet 51:A108.

Xu T, Bianco P, Fisher LW, Longenecker G, Smith E, Goldstein S, Bonadio J, Boskey A, Heegaard AM, Sommer B, Satomura K, Dominguez P, Zhao C, Kulkarni AB, Robey PG, Young MF. 1998. Targeted disruption of the biglycan gene leads to an osteoporosis-like phenotype in mice. Nat Genet 20:78–82.